57

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,538	06/30/2003	Yves Jacob	3495.0188-01	8265

22852 7590 03/29/2006

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,538	JACOB	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *1-42,51,52 and 54-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-50 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *May 11, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence letter*.

DETAILED ACTION

This is to acknowledge the preliminary amendment of sequence listing and drawing submitted on December 12, 2003. They have been accepted and entered.

Sequence requirements

This application contains sequence disclosures in **Figs. 1A to 1E** that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules about these sequences in Figs. 1A-1E is required in response to this Office Action. A complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Election/Restrictions

1. Applicant's election with traverse of group IV, claims 43-50 and 53 in the reply filed on 01/19/2006 is acknowledged. The traversal is on the ground(s) that there is not extra burden for searching the entire application. This is not found persuasive because the other groups of inventions in the application cover many polynucleotides that encode several structurally and functionally different fusion proteins other than the claimed polypeptide of lyssavirus glycoprotein as claims 43-50 and 53 drafted. Moreover, the polynucleotide and polypeptide are structurally and functionally different molecules; they have different status of art and require different searches. The patentability of a polypeptide cannot be determined by searching a polynucleotide. Especially, the claimed polynucleotide in other groups encodes structurally different polypeptide in that it comprises other nucleotide sequence besides the glycoprotein of lyssavirus. The distinctions of different inventions are also exhibited by the different searching

requirements. For example, searching a polypeptide encoding lyssavirus glycoprotein does not require search of a polynucleotide encoding a fusion protein comprising lyssavirus and a parasite or a tumor antigen.

2. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 43-50 and 53 are considered.

Information Disclosure Statement

4. The information disclosure statement regarding to the reference by Editorial, in Vaccine published on 1996, vol. 14, pp. 579-732, filed on May 11, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of said document. Therefore, it has been placed in the application file, but the information referred to therein has not been considered.

5. In the instant case, the examiner has only found the fist page of the reference, and the rest of pages are missing from the file. Applicants are required to submit the copies of all pages of this reference.

Priority

6. It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/549,519, filed 04/14/2000. A reference to the prior application(s) must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications.

7. If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its

inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. In the instant case, claim 43 is confusing because it is unclear whether the structure of the claimed polypeptide is only encoded by the nucleotide sequence encoding the partial glycoprotein or a polynucleotide of the entire carrying plasmid or vector DNA sequence. If it is in the second situation, the metes and bounds of claimed polynucleotide are not defined. In the instant case, specification has been carefully reviewed; it lacks the clear definition what the claimed carrier is while the specification only gives some examples related to the plasmid or viral vector etc. This affects the dependent claims 44-46. Pease clarify.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 44-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

13. Whether the applicants have the possession of claimed invention is related to the factors set forth below: 1). Level of skill in the art; 2). Method of making it; 3). Complete or partial structure; 4). Physical and/or biological properties; and 5). Correlation between structure and function

14. The state of art considers an immunogenic polypeptide or an immunogenic composition as a composition comprising an immunogenic polypeptide, wherein the polypeptide is either expressed by the recombinant DNA technique or synthesize as an antigen polypeptide that is specifically encoded by a target antigen sequence rather than the entire DNA sequence including the expression vector and said gene inserted into the vector. The state of art has never taught an immunogenic composition is made by plasmid or viral vector polypeptide. The specification of the current application only teaches the structure of lyssavirus glycoprotein that is expressed by the vector (carrier), but it lacks of description regarding to the structure of the polypeptide encoded by entire plasmid or viral vector polynucleotide sequence. The specification does not describe the physical and biological function as well as the relationship between them.

15. MPEP cites: "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs. Inc., 525 U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)." In the instant case, there is no any reduction to practice the claimed polypeptide encoded by a polynucleotide sequence of carrier molecule.

16. Therefore, it concluded that the applicants do not have a possession for the claimed invention.

17. Claims 46 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having an immunogenic composition comprising a glycoprotein polypeptide of the CVS, GT1 strain of lyssavirus that is able to induce response, does not reasonably provide enablement for having an immunogenic composition comprising a polypeptide encoded by a polynucleotide comprising the entire sequence of plasmid or viral vector in addition to the sequence encoding said lyssavirus glycoprotein polypeptide that is able to induce a protective immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

18. The test of an enablement or scope of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the application coupled with information known in the art would render undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988), which are set forth bellow:

19. 1). Nature of invention; 2). Scope of claims; 3). State of art; 4). Unpredictability; 5). Level of skill; 6). Number of working examples and 7). Amount of guidance presented in the specification.

20. The nature of invention is directed to a recombinant polypeptide comprising glycoprotein Site III of lyssavirus rather than the entire glycoprotein of lyssavirus, wherein the polypeptide is expressed by a recombinant plasmid DNA or vector. The polypeptide is also disclosed to be used as an immunogenic composition capable of inducing an immune response. However, the scope of the claims read on an immunogenic composition comprising a polypeptide encoded by the entire polynucleotide sequence of said plasmid or vector and it is claimed to able to induce a cellular and humoral immune response, especially, a protective immune response against any or all lyssaviruses.

21. The state of art considers an immunogenic polypeptide as an individual antigen polypeptide that is either expressed by the recombinant DNA technique or synthesized one. Such antigen polypeptide antigen has never been considered as a polypeptide encoded by the entire plasmid DNA. The state of art has never taught an immunogenic composition is made by such polypeptide. The specification of the current application only teaches the structure of lyssavirus glycoprotein that is expressed by the vector comprising the partial glycoprotein. It does not teach that the polypeptide is encoded by entire plasmid or viral vector polynucleotide sequence. The specification does not describe the physical and biological function as well as the relationship between them.

22. Moreover, state of the art also teaches that the sequence of the glycoprotein gene among the lyssavirus shear only about 54.3% global similarity. The divergence affects particularly the rabbies antigenic sites involved in B-cell response and provides a molecular basis for the absence of cross-protection between different lyssaviruses as evidenced by Fekadu et al. (Vaccine 1988, Vol. 6, No. 6, pp. 533-539, see abstract) and Lafon et al. (Vaccine 1988, Vol. 6, No. 4, pp. 3652-368). Still further, the polypeptide of glycoprotein has not been reported to be able to treat any disease including lyssavirus and induce a protective immune response in any or all individual. Because Perri et al. teach that the protective rate for the glycoprotein of a rabies is only about from 40 to 80% ((Vaccine 1985, Vol. 3, pp. 325-332, see Table a). It is unpredictable whether a polypeptide of entire plasmid DNA can b used as an immunogenic composition for inducing an immune response or induce a detrimental effect cause by the polypeptide encoded by the plasmid DNA. It is also unpredictable whether such glycoprotein of one lyssavirus is capable of cross reacting with any or all lyssaviruses and treating any or all kind of lyssavirus infection or even inducing a protective immune response against any lyssavirus.

23. Regarding to the cross immune response and protection, specification does neither teach nor give any adequate guidance of the inventions that read on using the polypeptide either encoded by the partial glycoprotein of a lyssavirus or by an entire plasmid DNA sequence.

24. Given the above analysis of the factors which the courts have determined are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

26. Claims 43 and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by Jallet et al. (J. Virol. Jan. 1999, Vol. 73, No. 1, pp. 225-233).

27. Jallet et al. disclose a polypeptide expressed by a carrier plasmid, wherein the plasmid comprising a polynucleotide sequence encoding only a part of glycoprotein including the lyssavirus Site III rather than the entire sequence of glycoprotein (See Fig. 1 and 2nd column of page 228). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims 43-44 and 47-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Metbtsoin et al. (J. Virol. 1995, vol. 69, pp. 3, pp. 1444-1451).

30. Metbtsoin et al. teach several recombinant chimeric glycoprotein encoded by a recombinant polynucleotide of vaccinia virus, wherein the chimeric glycoproteins

comprises either the site III or ectodomain of RV glycoprotein from - 9 to 430 that is fused with another heterlogous transmembrane and cytoplasmic domains of Eth-16 virus G protein (Se Figs. 1-2). After transfecting a host BSR cells, the recombinant chimeric glycoprotein is expressed and detected by an antibody. The recombinant glycoproteins all comprise the Site III and the entire particle is isolated from the supernatant as a SDI-CAT particles.

31. Claims 47-49 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Wunner et al. (Ann. Inst. Pasteur/Virol. 1985, Vol. 136^{E}, pp. 353-362).

32. Wunner et al. teach to an immunogenic composition comprising peptide antigen Cr5 (324-376) that covers the site III amino acid residues from 330-338 of glycoprotein of rabies virus and Fruedend's adjuvant and a method for using said immunogenic composition to induce an immune response in mice (See pages 355-357). The immune response include T cell immune response and humoral immune response. Therefore, the claimed invention is anticipated by the cited reference.

33. Claims 47-49 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Tordo et al. (Virol. 1993, Vol. 194, pp. 59-69).

34. Tordo et al. teach an isolated glycoprotein of lyssavirus- Mokola virus. The said glycoprotein is encoded by the nucleotide covering the Site III site rather than the entire glycoprotein gene sequence of said Mokola virus (See Figs. 1, 2, 6), which is constructed into the carrier plasmid and recombinant baculovirus vectors, expressed and purified (See pages 60-65 and Figs. 3-4). Torodo et al. also teach that said glycoprotein is prepared as subunit vaccine to induce an immune response, even a protective immune response in mice (see pages 65-67). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 103

35. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

36. Claims 47-49 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bahloul et al. (Vaccine 1998, Vol. 16, No. 4, pp. 417-425) and Wojczyk et al. (Protein expression and purification 1996, Vol. 7, pp. 183-193).

37. Bahloul et al. disclose a polypeptide expressed by a carrier plasmid, wherein the plasmid comprising a polynucleotide sequence encoding only a part of glycoprotein including the lyssavirus Site III rather than the entire sequence of glycoprotein (See Fig. 1 and 2nd column of page 228). Bahloul et al. teach that administration of a plasmid encoding said truncated glycoprotein into animal induces both cellular as well as humoral immune response. Moreover, said immune response can protect the mice from the homologous virus challenge (see entire document, especially Fig.s 1-4 and table 1-2). Bahloul et al. do not teach to said polypeptide to induce an immune response.

38. Wunner et al. teach to an immunogenic composition comprising peptide antigen Cr5 (324-376) that covers the site III amino acid residues from 330-338 of glycoprotein of rabies virus and Fruedend's adjuvant. Wunner et al. also teach a method for using said immunogenic composition to induce an immune response in mice (See pages 355-357). The immune response include T cell immune response and humoral immune response.

39. Wojcozyk et al. particularly teach how to isolate recombinant Rabies virus glycoprotein by constructing the rabies glycoprotein with a tag, expressing it as an affinity-tagged secreted forms, and purifying it through different kinds of columns (See entire document).

40. Therefore, it would have been obvious for a person with ordinary skill in the art to be motivated by the cited reference, in order to use a god immunogenic polypeptide from rabies virus to produce a significant immune response, to use the method taught by Wojcozyk et al. to purifying the right portion of glycoprotein of rabies disclosed by Jallet et al. because said portion of glycoprotein of rabies is already demonstrated to exhibit a good immune response against rabies infection in either DNA form evidenced by Bahloul et al. or in polypeptide form as taught by Wunner et al.

41. As there are no unexpected results have been provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results.

42. Claims 47-49 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jallet et al. (J. Virol. 1999, Vol. 73, no. 1, pp. 225-233), Wunner et al. (Ann. Inst. Pasteur/Virol. 1985, Vol. 136^{E}, pp. 353-362) and Wojczyk et al. (Protein expression and purification 1996, Vol. 7, pp. 183-193).

43. Jallet et al. disclose a polypeptide expressed by a carrier plasmid, wherein the plasmid comprising a polynucleotide sequence encoding only a part of glycoprotein including the lyssavirus Site III rather than the entire sequence of glycoprotein (See Fig. 1 and 2^{nd} column of page 228). Jallet et al. teach that administration a plasmid encoding said truncated glycoprotein into animal induce both cellular as well as humoral immune response. Moreover, said immune response can protect the mice from the homologous virus challenge (Figs. 1-6). Jallet et al. don't teach to said polypeptide to induce an immune response.

44. Wunner et al. teach to an immunogenic composition comprising peptide antigen Cr5 (324-376) that covers the site III amino acid residues from 330-338 of glycoprotein of rabies virus and Fruedend's adjuvant and a method for using said immunogenic composition to induce an immune response in mice (See pages 355-357). The immune response include T cell immune response and humoral immune response.

45. Wojcozyk et al. particularly teach how to isolate recombinant Rabies virus glycoprotein by constructing the rabies glycoprotein with a tag, expressing it as an affinity-tagged secreted forms, and purifying it through different kinds of columns (See entire document).

46. Therefore, it would have been obvious for a person with ordinary skill in the art to be motivated by the cited reference, in order to use a god immunogenic polypeptide from rabies virus to produce a significant immune response, to use the method taught by Wojcozyk et al. to purifying the right portion of glycoprotein of rabies disclosed by Jallet et al. because said portion of glycoprotein of rabies is already demonstrated to exhibit a good immune response against rabies infection in either DNA form evidenced by Jallet et al. or in polypeptide form as taught by Wunner et al.

47. As there are no unexpected results have been provided, hence the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 7:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li

BAOQUN LI, MD
PATENT EXAMINER

Baoqun Li

Notice to Comply	Application No.	Applicant(s)	
	Examiner	Art Unit	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Sequence disclosures in Fig. 1 A and 1E

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY